## REMARKS

Claims 22, 24, 28-30, and 32-24 are pending in this application upon entry of this amendment. Claims 22 and 24 have been amended to more clearly recite the claimed invention. Claims 1-21, 23, 25-27 and 31 have been canceled without prejudice. Applicants reserve the right to file one or more continuation or divisional applications to any canceled subject matter. No new matter has been added.

## I. The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Claims 22, 24-30, and 32-34 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office Action alleges the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

More particularly, the Office Action alleges that gene therapy at the time of the claimed invention was not well developed and was allegedly unpredictable. The Office Action further alleges that targeting to particular tissues was unpredictable. The Office Action does acknowledge, however, that the specification supports intravenous administration to target the liver. Without acquiescing to the merits of the Examiner's allegations, Applicants have amended the claims to recite that the composition is to treat fibrosis disorders of the liver and that the composition is administered intravenously.

The Office Action also alleges that claim 24 encompasses any therapeutic gene as written. According to the Office Action, the present invention is only enabled for MMP-8 and that the specification fails to enable for various therapeutic proteins. The Office Action further alleges that the function of a protein is unpredictable based on amino acid sequence and that amino acid changes can yield unpredictable results in a protein's function.

Applicants respectfully submit that the claims have been amended to overcome the rejection. The invention encompasses adenoviral vectors useful for their effect on fibrosis. Fibrosis involves the upregulation of multiple types of collagen. Metalloproteases degrade

collagen, with each metalloprotease capable of degrading multiple types of collagen. Accordingly, each of the claimed metalloproteases is useful in degrading the increased presence of collagen in a fibrotic liver. Furthermore, as the specification states, the truncated receptor for TGF-$\beta$ type II is useful to re-establish normal liver function. The claims, as amended, recite delivering to the liver increased recombinant expression of a select group of genes. The claims recite an adenoviral composition to increase their expression and subsequent activity in fibrotic livers. The example provided in the specification illustrates the success of the claimed invention in increasing the presence of expressed proteins in a fibrotic liver through a recombinant adenovirus. The use of a DNA sequence encoding a gene other than MMP-8 will still result in increased expression of that gene in the liver, which will yield a positive effect on the fibrotic liver. Therefore, it is respectfully submitted that the genes provided other than MMP-8 are not unpredictable in their effect and will not create undue experimentation. Accordingly, Applicants respectfully request that this rejection be withdrawn.

For at least the above reasons, Applicants respectfully submit that the rejection of claims 22, 24-30, and 32-34 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement should be reconsidered and withdrawn.

## II. The Rejection under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 22 and 28 are rejected on pages 12-13 under 35 U.S.C. § 103(a) as obvious over Fernandez *et al.* (*Surgery*, 124: 129-136, 1998) ("Fernandez") in view of Hasty *et al.* (*J Biol Chem.*, 265: 11421-11424, 1990) ("Hasty").

Claims 22 and 33 are rejected on pages 14-15 under 35 U.S.C. § 103(a) as obvious over Baker *et al.* (*Matrix Biology* 15: 383-395, 1996 ("Baker").

The Office Action alleges that Fernandez *et al.* disclose a MMP-3 adenovirus under a CMV promoter for transfecting human saphenous vein grafts at $1x10^9$ pfu. The Office Action relies on Hasty *et al.* to disclose the sequence for MMP-8.

The Federal Circuit has set forth three basic criteria that must be met to establish a case of *prima facia* obviousness. First, there must have been at the time of the invention a motivation to combine or modify the teachings of the references cited. *Ecolochem, Inc. v. Southern*

*California Edison Company*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (holding obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination); *see also In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (holding that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art). Second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious. *In re Royka*, 490 F.2d 488 (CCPA 1974) (holding that to establish *prima facia* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (holding that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure). Third, there must have been at the time of the invention a reasonable expectation of success. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-1208 (Fed. Cir. 1991), *cert. denied* 502 U.S. 856 (1991) (holding that obviousness requires references to show that there was, at the time of the invention, a reasonable expectation of success).

The U.S. Supreme Court has ruled in a unanimous opinion that a "narrow" and "rigid" TSM [teaching, suggestion, motivation] test is not the proper application of the non-obviousness doctrine of Section 103(a) of the Patent Act. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). According to the Supreme Court, "[t]o facilitate review, [the obviousness] analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ." The Court further elucidated, "[a] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." "There is no necessary inconsistency between the [teaching, suggestion, motivation] test and the Graham analysis. But a court errs where it transforms general principle into a rigid rule limiting the obviousness inquiry." The Federal Circuit stated that the test for *prima facie* obviousness in an invention concerning chemical

compounds "is consistent with the legal principles enunciated in *KSR*," and thus, "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a *prima facie* obviousness of a new claimed compound." *Takeda Chemical Industries, LTD et al. v. Alphapharm PTY., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007).

The claims, as amended, recite compositions to treat liver fibrosis that are administered intravenously. Fernandez *et al.* and Hasty *et al.* alone or in combination fail to disclose or suggest a composition for intravenous administration to treat liver fibrosis. Indeed, Fernandez *et al.* disclose a composition that is supplied to a segment of excised saphenous vein. Hasty *et al.* disclose MMP-8 is a metalloprotease produced by neutrophils. Both of the references are silent with regard to the claimed compositions including a therapeutically effective amount of unitary doses of viral particles of recombinant adenoviral vectors for intravenous administration to treat liver fibrosis. Indeed, the references alone or in combination fail to disclose or suggest composition, wherein the adenoviral vectors comprise an adenoviral genome of serotype Ad5 with deletions at E1 and inserted with a DNA sequence regulated by a ubiquitous promoter, a tissue-specific promoter, or a combination thereof, and wherein the DNA sequence encodes for a therapeutic protein for the treatment of hepatic fibrotic disorders. Accordingly, the combination of references fails to suggest each and every element of the claimed invention. *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003).

With regard to claim 28, Fernandez *et al.* disclose an *ex vivo* method of increasing MMP-3 expression. Fernandez does not disclose or suggest *in vivo* application and more importantly does not disclose or suggest intravenous administration. Hasty *et al.* fail to remedy these deficiencies. Accordingly, no combination of the references teaches or suggests every element recited in claim 28.

With regard to the rejection of claims 22 and 33over Baker *et al.*, Applicants submit that Baker *et al.* disclose MMP-9 transfection from the pAL119 vector into smooth muscle cells and MCF-7 cells on coverslips. Baker *et al.* do not disclose or suggest administering a composition intravenously for recombinant expression in the liver. Indeed, the Office Action acknowledges that Baker *et al.* do not disclose a dosing range of $1x10^7$ pfu to $1x10^9$ pfu. The Office Action

alleges, however, that the 3-1000 pfu/cell range disclosed by Baker *et al.* allows for routine determination of an effective dose. It is respectfully submitted that Baker *et al.* disclose bathing cells *in vitro* in an adenovirus. Baker *et al.* do not disclose or suggest an effective dose for intravenous administration and provide no suggestion or guidance on methods to determine an effective dose to treat hepatic fibrosis when administered intravenously. Accordingly, Baker *et al.* fail to suggest the claimed composition or its method of use.

Therefore, Applicants respectfully request that the rejection of claims 22, 28, and 33 under 35 U.S.C. § 103(a) should be withdrawn.

## III. Conclusions

It is respectfully submitted that the rejections to the claims have been overcome. Should the Examiner disagree, Applicants respectfully request a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

Except for issues payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

Respectfully submitted,
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